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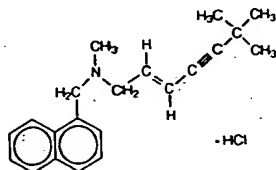
REFERENCE®

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## DESCRIPTION

Lamisil® (terbinafine hydrochloride tablets) Tablets contain the synthetic allylamine antifungal compound terbinafine hydrochloride.

Chemically, terbinafine hydrochloride is (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride. The empirical formula  $C_{21}H_{28}ClN$  with a molecular weight of 327.90, and the following structural formula:



Terbinafine hydrochloride is a white to off-white fine crystalline powder. It is freely soluble in methanol and methylene chloride, soluble in ethanol, and slightly soluble in water.

### Each tablet contains:

**Active Ingredients:** terbinafine hydrochloride (equivalent to 250 mg base)

**Inactive Ingredients:** colloidal silicon dioxide, NF; hydroxypropyl methylcellulose, USP; magnesium stearate, NF; microcrystalline cellulose, NF; sodium starch glycolate, NF

## CLINICAL PHARMACOLOGY

### Pharmacokinetics

Following oral administration, terbinafine is well absorbed (>70%) and the bioavailability of Lamisil® (terbinafine hydrochloride tablets) Tablets as a result of first-pass metabolism is approximately 40%. Peak plasma concentrations of 1 µg/mL appear within 2 h after a single 250 mg dose; the AUC (area under the curve) is approximately 4.56 µg·h/mL. An increase in the AUC of terbinafine of less than 20% is observed when Lamisil® is administered with food. No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been reported. In patients with renal impairment (creatinine clearance ≤50 mL/min) or hepatic cirrhosis, the clearance of terbinafine is decreased by approximately 50% compared to normal volunteers. No effect of gender on the blood levels of terbinafine was detected in clinical trials. In plasma, terbinafine is >99% bound to plasma proteins and there are no specific binding sites. At steady-state, in comparison to a single dose, the peak concentration of terbinafine is 25% higher and plasma AUC increases by a factor of 2.5; the increase in plasma AUC is consistent with an effective half-life of ~36 hours. Terbinafine is distributed to the sebum and skin. A terminal half-life of 200-400 h may represent the slow elimination of terbinafine from tissues such as skin and adipose. Prior to excretion, terbinafine is extensively metabolized. No metabolites have been identified that have antifungal activity similar to terbinafine. Approximately 70% of the administered dose is eliminated in the urine.

### Microbiology

Terbinafine hydrochloride is a synthetic allylamine derivative. Terbinafine hydrochloride is hypothesized to act by inhibiting squalene epoxidase, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. *In vitro*, mammalian squalene epoxidase is only inhibited at higher (4000 fold) concentrations than is needed for inhibition of the dermatophyte enzyme. Depending on the concentration of the drug and the fungal species test *in vitro*, terbinafine hydrochloride may be fungicidal. However, the clinical significance of *in vitro* data is unknown. Terbinafine has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

- Trichophyton mentagrophytes
- Trichophyton rubrum
- Candida albicans
- Epidermophyton floccosum
- Scopulariopsis brevicaulis

The following *in vitro* data are available, but their clinical significance is unknown. *In vitro*, terbinafine exhibits satisfactory MICs against most strains of the following microorganisms; however, the safety and efficacy of terbinafine in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

- Candida albicans
- Epidermophyton floccosum
- Scopulariopsis brevicaulis

## CLINICAL STUDIES

The efficacy of Lamisil® (terbinafine hydrochloride tablets) Tablets in the treatment of onychomycosis is illustrated by the response of patients with toenail and/or fingernail infections who participated in three US/Canadian placebo-controlled clinical trials.

Results of the first toenail study, as assessed at week 48 (12 weeks of treatment with 36 weeks follow-up after completion of therapy), demonstrated mycological cure in 79% of patients, effective treatment in 75% of the patients, and mycological cure plus-clinical cure in 59% of the patients. The mean time to overall success was approximately 10 months for the first toenail study and 4 months for the fingernail study. In the first toenail study, for patients evaluated at least six months after achieving clinical cure and at least one year after completing Lamisil® therapy, the clinical relapse rate was approximately 15%.

The pathogenic role of the non-dermatophytes cultured in the presence of dermatophytic onychomycosis has not been established. The clinical significance of this association is unknown.

Results of the fingernail study, as assessed at week 24 (6 weeks of treatment with 18 weeks follow-up after completion of therapy), demonstrated mycological cure in 79% of patients, effective treatment in 75% of the patients, and mycological cure plus-clinical cure in 59% of the patients. The mean time to overall success was approximately 10 months for the first toenail study and 4 months for the fingernail study. In the first toenail study, for patients evaluated at least six months after achieving clinical cure and at least one year after completing Lamisil® therapy, the clinical relapse rate was approximately 15%.

## INDICATIONS AND USAGE

Lamisil® (terbinafine hydrochloride tablets) Tablets are indicated for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium) (see **DOSE AND ADMINISTRATION** and **CLINICAL STUDIES**).

## CONTRAINDICATIONS

Lamisil® (terbinafine hydrochloride tablets) Tablets are contraindicated in individuals with hypersensitivity to terbinafine or to any other ingredients of the formulation.

## WARNINGS

Rare cases of symptomatic hepatobiliary dysfunction including cholestatic hepatitis have been reported. Treatment with Lamisil® (terbinafine hydrochloride tablets) Tablets should be discontinued if hepatobiliary dysfunction develops (see **PRECAUTIONS** and **ADVERSE REACTIONS**). There have been isolated reports of serious skin reactions (e.g., Stevens-Johnson Syndrome and toxic epidermal necrolysis). If progressive skin rash occurs, treatment with Lamisil® should be discontinued.

## PRECAUTIONS

### General

Changes in the ocular lens and retina have been reported following the use of Lamisil® (terbinafine hydrochloride tablets) Tablets in controlled trials. The clinical significance of these changes is unknown.

Hepatic function (hepatic enzyme) tests are recommended in patients administered Lamisil® (terbinafine hydrochloride tablets) Tablets for more than six weeks or in those who develop unexplained persistent nausea, anorexia, or fatigue or jaundice, dark urine, or pale stools (see **WARNINGS**).

In patients with either pre-existing liver disease or renal impairment (creatinine clearance ≤50 mL/min), the use of Lamisil® has not been adequately studied, and therefore, is not recommended (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

Transient decreases in absolute lymphocyte counts (ALC) have been observed in controlled clinical trials. In placebo-controlled trials, 8/465 Lamisil®-treated patients (1.7%) and 3/137 placebo-treated patients (2.2%) had decreases in ALC to below 1000/mm<sup>3</sup> on two or more occasions. The clinical significance of this observation is unknown. However, in patients with known or suspected immunodeficiency, physicians should consider monitoring complete blood counts in individuals using Lamisil® therapy for greater than six weeks.

Isolated cases of severe neutropenia have been reported. These were reversible upon discontinuation of Lamisil®, with or without supportive therapy. If clinical signs and symptoms suggestive of secondary infection occur, a complete blood count should be obtained. If the neutrophil count is <1,000 cells/mm<sup>3</sup>, Lamisil® should be discontinued and supportive management started.

### Drug Interactions

*In vitro* studies with human liver microsomes showed that terbinafine does not inhibit the metabolism of tolbutamide, ethinylestradiol, ethoxycoumarin, and cyclosporine. *In vivo* drug-drug interaction studies conducted in normal volunteers; subjects showed that terbinafine does not affect the clearance of antipyrine, digoxin, and the antihistamine terfenadine. Terbinafine decreases the clearance of intravenously administered caffeine by 15%. Terbinafine increases the clearance of cyclosporine by 15%.

Terbinafine clearance is increased 100% by rifampin, a CYP450 enzyme inducer, and decreased 33% by cimetidine, a CYP450 enzyme inhibitor. Terbinafine exposure (AUC) is increased 16% by terfenadine. Terbinafine clearance is unaffected by cyclosporine.

There is no information available from adequate drug-drug interaction studies with the following classes of drugs: oral contraceptives, hormone replacement therapies, hypoglycemics, theophyllines, phenytoins, thiazide diuretics, beta-blockers, and calcium channel blockers.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 28-month oral carcinogenicity study in rats, a marginal increase in the incidence of liver tumors was observed in males at the highest dose level, 60 mg/kg/day (3.6x the Maximum Recommended Human Dose (MRHD) based on body surface area (BSA)). There was no dose-related trend and the mid-dose male rats (20 mg/kg/day, 1.0x the MRHD based on BSA) did not have any tumors. No increased incidence in liver tumors was noted in female rats at dose levels

wide range of *in vivo* studies in mice, rats, and dogs. *In vitro* studies using rat hepatocytes suggest that the development of the high-dose male rats may be associated with proliferation, and support the conclusion of a specific finding. *In vivo* investigations of the effects of Lamisil® on liver ultrastructure, hepatic cytochrome P-450, proliferation assessed morphologically (peroxisomal enzymes) in mice, rats, and dogs. The effects of Lamisil® and two known hepatic morphological and peroxisomal activities were also evaluated *in vivo* in male primary hepatocyte cultures from mice and from monkeys. The results of the studies indicated that oral administration of Lamisil® (day) resulted in peroxisome proliferation; these effects did not occur in mice, dogs, or in *in vitro* studies indicated that peroxisome proliferation occurred in rat hepatocytes, but not in mouse hepatocytes.

Systemic exposure to Lamisil®, assessed as state plasma unbound fraction area under the curve for terbinafine and metabolites, was comparable for male and female rats, respectively, at 10 µg·h/mL for male and female mice, respectively, comparable to the high doses in the carcinogenicity studies. In human subjects at the MRHD (a daily dose of 250 mg), the unbound AUC was 0.17, resulting safety margins for human systemic exposure (AUC unbound), 17 to 21 and 24 to 28, respectively. The results of a variety of *in vitro* (mutagenicity, DNA repair in rat hepatocytes, Chinese hamster fibroblasts, chromosome sister chromatid exchanges in Chinese hamster ovary cells, and *in vivo* (chromosome aberration, micronucleus test in mice) genotoxicity studies demonstrated the absence of tumor-initiating activity.

Oral reproduction studies in rats at doses up to 12x the MRHD (a daily dose of 250 mg) reveal any specific effects on fertility or parameters. Intravaginal application of terbinafine hydrochloride at 150 mg/day in pregnant rats increased the incidence of abortions or preterm births but did not affect fetal parameters.

### Pregnancy

**Pregnancy Category B:** Oral reproduction studies performed in rabbits and rats at doses up to 12x the MRHD, in rabbits based on BSA, and have revealed no evidence of fertility or harm to the fetus due to terbinafine. However, no adequate and well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are always predictive of human response, the use of Lamisil® is not recommended during pregnancy.

### Nursing Mothers

After oral administration, terbinafine is excreted in milk of nursing mothers. The ratio of terbinafine in plasma is 7:1. Treatment with Lamisil® is not recommended in nursing mothers.

### Pediatric Use

The safety and efficacy of Lamisil® have not been established in pediatric patients.

## ADVERSE REACTIONS

The most frequently reported adverse reactions in the three US/Canadian placebo-controlled clinical trials are listed in the table below. The adverse reactions were gastrointestinal symptoms (nausea, vomiting, and abdominal pain), liver test abnormalities (elevated ALT, AST, and GPT), and taste disturbances. Adverse events were mild to moderate and discontinued from study.

Adverse Reaction	Lamisil® (n=120)	Placebo (n=120)
Headache	10	8
Nausea	12	10
Vomiting	5	3
Abdominal pain	8	6
Diarrhea	7	5
Dyspepsia	6	4
Flatulence	4	3
Constipation	3	2
Stomach pain	2	1
Loss of taste	1	0
Increased ALT	1	0
Increased AST	1	0
Increased GPT	1	0

### Headache

### Gastrointestinal Symptoms

### Diarrhea

### Dyspepsia

### Abdominal Pain

### Nausea

### Flatulence

### Constipation

### Stomach pain

### Loss of taste

### Increased ALT

### Increased AST

### Increased GPT

Rest Available Copy

is the first entirely synthetic HMG and is in part structurally distinct from the therapeutic class of statins. It is white to pale yellow, hygroscopic and soluble in methanol and methanol/acetone.

estatin is metabolized in the liver primarily via hydroxylation of the indole ring at the 5- and 6-positions, acetylation and beta-oxidation of the side chain, also occurs. The hydroxy metabolites have some pharmacologic activity, but do not circulate in the blood. Both enantiomers

though frequently found in association with low HDL-C, elevated plasma TG has not been established as an independent risk factor for coronary heart disease. The independent effect of raising HDL-C or lowering TG on the risk for coronary and cardiovascular morbidity and mortality has not been established. In the Coronary Atherosclerosis Project, atherosclerosis observed at autopsy was related to both the lipoprotein and coronary atherosclerosis. Study (CASA), the effect of Lescol® (fluvastatin sodium) therapy on coronary atherosclerosis was assessed by quantitative coronary angiography (QCA) in patients with coronary artery disease and mild to moderate hypercholesterolemia. The LDL-C levels 115-190 mg/dL in this randomized